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SPECIAL ANNOUNCEMENT

THE THIRD INTERNATIONAL STANDARD FOR CORTICOTROPHIN AND AN INTERNATIONAL WORKING STANDARD FOR CORTICOTROPHIN

A new standard, the Third International Standard for Corticotrophin has just been established with a defined potency of 5 (international units) i.u. per ampoule. A memorandum describing details of the standard and the international collaborative assay will be published in the near future.[1]

Until a few years ago most commercial preparations of corticotrophin were of crude material. With the advent of purer preparations of much higher potency, it soon became clear that these purer preparations could not satisfactorily be assayed against the Second International Standard for Corticotrophin which was of crude material. In all bioassays it is desirable to compare the substance under test with a standard of roughly equivalent potency and purity; for the assay of corticotrophin it is essential to do so. It was decided by the Expert Committee on Biological Standardization at its 11th Session in Geneva, 1957,[2] to replace the Second International Standard with a new one based on material of high potency.

This raised some difficult problems. The Second International Standard for Corticotrophin (crude material) had a potency of 1.14 i.u./mg. (by definition). The purer preparations of corticotrophin, when assayed against it by the adrenal ascorbic depletion method, gave potencies of 10-30 i.u./mg. if the standard and test doses were given intravenously, and potencies of 30-90 i.u. if the doses were given subcutaneously. The ratio of the potencies obtained by the intravenous (i.v.) and subcutaneous (s.c.) methods may vary from batch to batch, but is usually about 1 : 3. The reason for the i.v. : s.c. "potency ratio" is not clearly understood, but it may be associated with the method of preparation and the rate of destruction and absorption at the site of injection. A similar effect is also shown in man. Thus a given amount of corticotrophin of high purity gives a greater effect by subcutaneous than by intravenous administration, compared with crude corticotrophin.

A batch of material which had the most common i.v. : s.c. potency ratio (1 : 3) was chosen for the new standard. It was then necessary to decide which route of administration was to be used in the assays determining the potency. Because of the complexity of factors influencing the s.c. assay (rate of absorption and destruction), it is generally believed that i.v. assays probably give a truer measure of corticotrophin active principle than s.c. assays. However, most of the corticotrophin at present used in clinical treatment is given subcutaneously or intramuscularly to the patient, much of it in the form of "delay" preparations, and clinicians have become accustomed to the clinical effect of the labelled unit. For this reason, nearly all preparations for clinical use are assayed by the s.c. method (which also gives more precise results than the i.v. method). For the sake of clinical continuity, therefore, it was decided[2] to determine the potency of the new standard by s.c. assay.

Corticotrophin intended for subcutaneous or intramuscular administration should be assayed by the s.c. method and *there will be no change in the clinical value of the unit of preparations given* subcutaneously or intramuscularly. Corticotrophin intended for intravenous administration should be assayed by the i.v. method. *In countries where manufacturers have hitherto assayed these preparations against a standard of low potency material, this will involve a change of the clinical value of the unit given intravenously such that about three times the number of units will need to be given to produce the same response.* In some countries this change has already been effected.[3]

This change in value of the unit in intravenous and *in vitro* assays will also affect academic endocrinologists and biochemists who use these assays to relate biological activity to a given quantity of corticotrophin. (A full discussion of the results of assays of the new standard by the i.v. and *in vitro* methods is available in the aforementioned memorandum.[1])

An arbitrary choice had to be made whether to change the value of the unit as used by the great majority of clinicians, or the value used by scientists; it was decided to maintain continuity for clinical practice. Though this change will cause some inconvenience to a minority of users, it is inevitable and due to progress in the purification of corticotrophin, and will ultimately lead to a more uniform labelling of corticotrophin throughout the world.

The International Working Standard

The traditional purpose of international standards is for the calibration of national standards. The assay of corticotrophin is difficult and relatively imprecise; the variability (sometimes unpredictable) of preparations is well known. The setting up of national standards of high potency material would be particularly laborious and costly and they might differ significantly in stability and other characteristics.

In order to ensure the maximum degree of uniformity throughout the world, an international Working Standard has also been established.[1] This is prepared from the same material and in precisely the same way as the Third International Standard. Samples of the Working Standard were included in the international collaborative assay, and the results show that these contained the same 5 i.u. per ampoule as the International Standard itself.

Sufficient ampoules of this international Working Standard are available to replace national and house standards for the routine control of corticotrophin and to supply research laboratories with working standards. Supplies are available on written request to—The Department of Biological Standards, National Institute for Medical Research, Mill Hill, London, N.W.7.

REFERENCES

1. BANGHAM, D. R., MUSSETT, M. V. AND STACK-DUNNE, M. P.: *Bull. WHO* in press.
2. World Health Organization, Expert Committee on Biological Standardization: Eleventh report, WHO Technical Report Series No. 147, World Health Organization, Geneva, 1958, p. 8.
3. Annotation: *Brit. Med. J.*, 1: 765, 1958.